Remarks

Based on the amendments to the claims and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

I. Objections to the Specification

In the Office Action at pages 3 and 4, section 6, the specification is objected to for failing to contain a specific reference to the priority application. Applicants have amended the specification to insert the specific reference. Applicants respectfully request withdrawal of this objection.

In the Office Action at pages 3 and 4, section 6, the inclusion of "viral" and "bacteriophage" in a group of cells or tissues is objected to as it is alleged that "viruses and bacteriophages are not cells or tissues." The specification has been amended to separately list viruses and bacteriophages. Applicants respectfully request withdrawal of this objection.

II. Status of the Claims

In the present amendment, claims 57-69 are canceled, claims 8 and 56 are amended, and new claims 70-75 are presented. Claims 8-13, 56, and 70-75 are pending in this application with claim 8 being the sole independent claim.

Support for the amendment to claim 8 can be found throughout the specification, *inter alia*, at page 12, lines 20-25, page 13, lines 1-20, page 15, lines 5-12, and in the Examples.

Support for the amendment to claim 56 can be found throughout the specification, *inter alia*, at page 20, lines 3-7.

Support for new claim 70 can be found throughout the specification, *inter alia*, at page 10, lines 4-8, and in the Examples.

Support for new claim 71 can be found throughout the specification, *inter alia*, at page 9, line 20 to page 10, line 3.

Support for new claim 72 can be found throughout the specification, *inter alia*, at page 20, lines 17-19.

Support for new claim 73 can be found throughout the specification, *inter alia*, in the Examples.

Support for new claim 74 can be found throughout the specification, *inter alia*, at page 20, lines 3-4.

Support for new claim 75 can be found throughout the specification, *inter alia*, at page 20, lines 3-4.

III. Summary of the Office Action

In the Office Action dated March 12, 2002, the Examiner made 10 objections and rejections of the specification and claims. Applicants respectfully offer the following remarks to overcome these rejections.

IV. The Objection to Claim 8 Is Moot

In the Office Action at page 4, section 7, claim 8 was objected to on grammatical grounds. Claim 8 has been amended rendering this objection moot. Applicants respectfully request withdrawal of this objection.

V. The Rejection of Claims 8-13, and 56 Under 35 U.S.C.§ 112, second paragraph, Must be Withdrawn

In the Office Action at page 4, section 8, claims 8-13, and 56 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Applicants respectfully request reconsideration and withdrawal of this rejection.

The Examiner alleges that claim 8 and dependent claims 9-13 and 56 are indefinite for the use of the phrase "crude preparation." The Examiner indicates "it is unclear what is to be encompassed by 'a crude preparation containing DNA.'" Claim 8 as amended no longer contains the language alleged to be indefinite. Applicants respectfully request reconsideration and withdrawal of this rejection.

In the Office Action at page 6, section 10, claim 56 has been alleged to be indefinite for the inclusion of viruses and bacteriophages in a list of items identified as tissues or cells. These items have been deleted from claim 56 and are separately claimed in newly presented claims 74 and 75. Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection.

VI. The Rejection of Claims 8-12 Under 35 U.S.C.§ 102(a) As Being Anticipated by Maudru Must be Withdrawn

In the Office Action at page 7, section 11, claims 8-12 have been rejected under 35 U.S.C. § 102(a) as being anticipated by Maudru, *et al.*, (*Journal of Virological*

Methods 66:247-261, July 1997, hereinafter "Maudru"). Applicant respectfully traverses this rejection.

A claimed invention is anticipated under 35 U.S.C. § 102 only if there is "[d]isclosure in a single piece of prior art of each and every limitation of a claimed invention." *Apple Computer, Inc. v. Articulate Systems, Inc.*, 234 F.3d 14, 20, 57 USPQ2d 1057, 1061 (Fed. Cir. 2000), *citing Electro Med. Sys. S.A. v. Cooper Life Sciences,* 34 F.3d 1048, 1052, 32 USPQ2d 1017, 1019 (Fed. Cir. 1994). Maudru does not disclose the invention as presently claimed. Accordingly, this rejection is improper and must be withdrawn.

Claim 8 is the sole independent claim. Claims 9-12 depend—directly or indirectly—from claim 8. Claim 8 is drawn to a method of synthesizing a DNA molecule from a preparation. As presently claimed, independent claim 8—and therefore all the dependent claims—requires that the preparation contain RNA and double-stranded DNA.

Maudru is concerned with eliminating background signals in RT-PCR (*see*, Abstract). Maudru discloses treating the product of an RT reaction with ribonuclease prior to the PCR step (*see*, page 248, right column, last paragraph). Treatment of the product with a ribonuclease results in a single-stranded DNA molecule and degradation of the RNA. At no point in time is there both RNA and double-stranded DNA present in the reaction mixture of Maudru. Since the cited art does not disclose each and every limitation of the presently claimed invention, Applicant respectfully requests reconsideration and withdrawal of this rejection.

VII. The Rejection of Claims 8-12 Under 35 U.S.C. § 102(b) As Being Anticipated by Don, et al. Must Be Withdrawn

In the Office Action at page 10, section 12, claims 8-12 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Don *et al.* (*Nucleic Acids Research* 21(3): page 783, 1993, hereinafter "Don *et al.*"). Applicants respectfully traverse this rejection.

A claimed invention is anticipated under 35 U.S.C. § 102 only if there is "[d]isclosure in a single piece of prior art of each and every limitation of a claimed invention." *Apple Computer, Inc. v. Articulate Systems, Inc.*, 234 F.3d 14, 20, 57 USPQ2d 1057, 1061 (Fed. Cir. 2000) *citing Electro Med. Sys. S.A. v. Cooper Life Sciences,* 34 F.3d 1048, 1052, 32 USPQ2d 1017, 1019 (Fed. Cir. 1994). Don *et al.* does not disclose the invention as presently claimed. Accordingly, this rejection is improper and must be withdrawn.

Claim 8 is the sole independent claim. Claims 9-12 depend—directly or indirectly—from claim 8. Claim 8 is drawn to a method of synthesizing a DNA molecule from a preparation. As presently claimed, independent claim 8—and therefore all the dependent claims—requires that the preparation contain RNA and double-stranded DNA.

Don is concerned with the synthesis of cDNA from mRNA and subsequent amplification of the cDNA (*see*, page 783, title). Don conducts an RT reaction on total RNA using an oligo dT primer (page 783, left column, third paragraph). After the first strand reaction, RNase H and *E. coli* DNA polymerase I are added. *Id.* The RNase H degrades the RNA and the DNA polymerase synthesizes the second strand. At no point in time is there both RNA and double-stranded DNA present in the reaction mixture of Don. Since the cited art does not disclose each and every limitation of the presently

claimed invention, Applicant respectfully requests reconsideration and withdrawal of this rejection.

VIII. The Rejection of Claims 57-59, and 62 Under 35 U.S.C. § 102(e) As Being Anticipated by Kenten, et al. Is Moot

In the Office Action at page 12, section 13, claims 57-59, and 62 have been rejected under 35 U.S.C. § 102(e) as being anticipated by Kenten, *et al.* (U.S. Patent No. 6,048,687 hereinafter "Kenten"). These claims have been canceled rendering this rejection moot. Applicant respectfully request withdrawal of this rejection.

IX. The Rejection of Claims 8-13 Under 35 U.S.C. § 103(a) As Being Obvious Over Maudru or Don Must Be Withdrawn

In the Office Action at page 14, section 14, claims 8-13 have been rejected under 35 U.S.C. § 103(a) as being obvious over Maudru or Don. Applicants respectfully traverse this rejection.

MPEP 2143.03 reads in pertinent part "[t]o establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art." (*citing In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974)). Applicants respectfully submit that the Examiner has failed to establish a *prima facie* case for the obviousness of the presently claimed invention and respectfully request reconsideration and withdrawal of this rejection as it may be applied to the present claims.

Claim 8 is the sole independent claim. Claims 9-13 depend—directly or indirectly—from claim 8. Claim 8 is drawn to a method of synthesizing a DNA molecule

from a preparation. As presently claimed, independent claim 8—and therefore all the dependent claims—requires that the preparation contain RNA and double-stranded DNA.

As discussed above, neither Maudru nor Don discloses a preparation containing both RNA and double-stranded DNA. Further, neither Maudru nor Don suggests a preparation containing both RNA and double-stranded DNA. Since the cited references do not teach or suggest the invention as claimed, this rejection is improper and must be withdrawn. Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection.

X. The Rejection of Claims 8-13 and 57-69 Under 35 U.S.C. § 103(a) As Being Obvious Over Schowalter, et al., Maudru and Sambrook, et al. Must Be Withdrawn

In the Office Action at page 16, section 15, claims 8-13 and 57-69 have been rejected under 35 U.S.C. § 103(a) as being obvious over Schowalter, *et al.* (*Analytical Biochemistry* 177:90-94, 1989, hereinafter "Schowalter"), Maudru and Sambrook, *et al.* (Molecular Cloning a Laboratory Manual, 2nd Edition, Cold Spring Harbor Laboratory Press, 1989, pages 1.33-1.52, hereinafter "Sambrook"). Applicants respectfully traverse this rejection.

MPEP 2143.02 reads in pertinent part "[t]he prior art can be modified or combined to reject claims as *prima facie* obvious as long as there is a reasonable expectation of success." (*citing In re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1985)). Applicants respectfully submit that the Examiner has failed to establish a *prima facie* case for the obviousness of the presently claimed invention and

respectfully request reconsideration and withdrawal of this rejection as it may be applied to the present claims.

Claims 57-69 have been canceled. Claim 8 is the sole independent claim. Claims 9-13 depend—directly or indirectly—from claim 8. Claim 8 is drawn to a method of synthesizing a DNA molecule from a preparation. As presently claimed, independent claim 8—and therefore all the dependent claims—requires that the preparation contain RNA and double-stranded DNA and that it be mixed with one or more DNA polymerases and one or more polypeptides having ribonuclease activity.

Schowalter discloses a method for generating labeled probes using PCR. As the Examiner acknowledges (Office Action, page 17, lines 9-10), Schowalter does not disclose the use of a ribonuclease in the amplification protocol. Further, the amplification reaction conducted by Schowalter is conducted on a DNA template with no mention being made of any RNA being present (*see*, page 90, *Protocol for PCR Labelling).* In the Office Action it is alleged that:

> Schowalter et al. teach that these methods obviate the need for CsCl gradient purification of the DNA template or other large scale methods of prior DNA preparation, thus they include synthesis from "crude preparations containing DNA", although they acknowledge that high background with spurious bands will result from the presence of contaminating sequences. *Office Action, page 17, first paragraph*

Maudru is then cited for the proposition that a high background signal could be eliminated by the incorporation of ribonuclease in the amplification reaction and Sambrook for the proposition that CsCl gradients are used to remove contaminants from DNA preparations. The Examiner concludes that one skilled in the art would be motivated to include a polypeptide having ribonuclease activity in the amplification

reaction of Schowalter in order to remove the residual RNA present in the preparation and thereby reduce the background signal.

Schowalter amplifies a genomic DNA template with primers designed to amplify a 769-bp fragment of the human factor IX gene. (*See*, page 92, right column, last paragraph). The DNA template is characterized as "extracted" (*see*, page 90, *Materials and Methods*, first paragraph) and Schowalter cites to another paper from the same lab for the extraction procedure (*see*, page 94, *References*, reference number 7, Gustafson, *et al.*, 1987, *Analytical Biochemistry* 165: 294-299). A copy of the Gustafson reference is provided.

During the preparation of the DNA used by Schowalter, prepared using the method of Gustafson, the issue of RNA contamination was considered. (*See*, Gustafson, page 295, right column). The solution was to include RNase in the extraction buffer if RNA contamination was observed by gel electrophoresis and ethidium bromide staining of the DNA preparation or if mRNA contamination was a concern. *Id.* Thus, the DNA used by Schowalter has either been examined and found not to contain RNA, or has been treated with RNase. Thus, one skilled in the art would not be motivated to combine the ribonuclease of Maudru with the amplification procedure of Schowalter because the issue of contaminating RNA had already been dealt with. Sambrook is a general teaching of methods to purify plasmid DNA and provides no motivation to combine the ribonuclease of Maudru with the amplification procedure of Schowlater.

One of skill in the art would have no reasonable expectation that adding ribonuclease to an amplification reaction mixture containing DNA *that had already been treated for RNA contamination*, would have the effect of reducing the background. Since

one of skill in the art would have had no reasonable expectation of success, Applicants respectfully submit that this rejection is improper and request its reconsideration and withdrawal.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicant therefore respectfully requests that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicant believes that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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Version with markings to show changes made

Please insert the following paragraph in the specification for the paragraph beginning at page 20, line 3.

Methods envisioned in accordance with the invention include nucleic acid synthesis, sequencing, labeling, and amplification from crude preparations of DNA from viruses, bacteriophages, and from any cell or tissue such as [viral, bacteriophage,] bacteria, insect, bird, fish, plant, yeast, prokaryotes, eukaryotes and mammals. Preparation of crude extracts of cells or tissues may be accomplished by standard procedures which allow[s] removal of at least some nucleic acids from the cell or tissue without the need for purification of the nucleic acids from the cells, tissue or cell/tissue debri, although nucleic acids may be isolated or purified or partially purified prior to use in accordance with the invention. Examples of such procedures include[s] lysis or disruption of cells or tissues by mechanical (heat, sonication, vortex with glass beads, etc.), enzymatic (lysozyme, etc.) or chemical (pH, salt, detergent, etc.) means. Alternatively, the cells and/or tissues may be used directly in the methods of the invention without prior manipulation (such as lysis, disruption etc.). The applications of the invention are numerous, including direct cloning from genomic DNA or cDNA, *in vitro* mutagenesis and engineering of DNA, analysis of allelic sequence variations, analysis of RNA transcript structure, genetic fingerprinting of forensic samples, autopsies, biopsies, and archeological samples, assays for the presence of infectious

agents, prenatal diagnosis of genetic diseases, genomic fingerprinting, and direct nucleotide sequencing of genomic DNA or cDNA, to name a few.

The claims have been amended as follows:

8. (Thrice amended) A method for synthesizing a nucleic acid molecule from a [crude] preparation [containing] comprising RNA and double-stranded DNA, said method comprising:

a) mixing the [crude] preparation [containing DNA wherein the DNA functions as a desired nucleic acid template,]with one or more DNA polymerases, and one or more peptides or polypeptides having ribonuclease activity; and

b) incubating said mixture under conditions sufficient to synthesize a nucleic acid molecule complementary to all or a portion of said template and sufficient to degrade single-stranded RNA.

56. (Amended) The method of claim 8, wherein said [crude] preparation [containing DNA] is from any cell or tissue selected from the group consisting of [virus; bacteriophage;] bacteria; insect; bird; fish; plant; yeast; prokaryote; eukaryote; and mammals.

Claims 57-69 are canceled.

New claims 70-75 are presented.